Scientists discover a novel mechanism leading to the inflammatory cytokine storm in COVID-19

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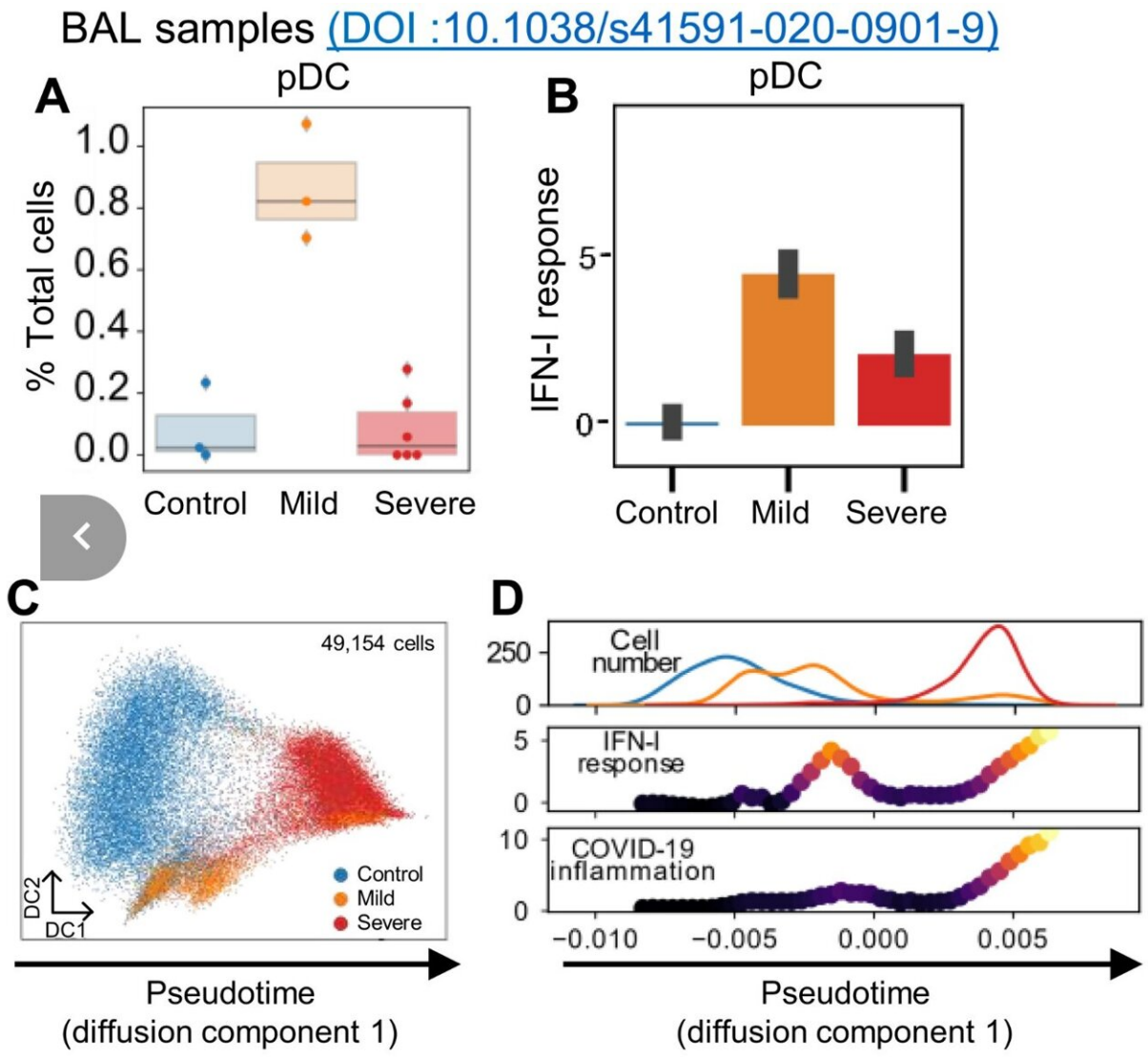

IFN-I response associated with pDCs precedes inflammatory response in macrophages from BAL fluids and lungs of patients with COVID-19. (A) Abundance of pDCs depending on disease state in BAL from DOI:10.1038/s41591-020-0901-9. (B) Abundance of IFN-I response for pDCs aggregated by disease state in BAL. (C) Inference of a pseudotime axis using diffusion maps for macrophage cells only from the BAL of healthy donors (HDs) and patients with mild or severe COVID-19. (D) Distribution of macrophage cells (top), IFN-I response signature (middle), and COVID-19 inflammatory signature (bottom) across the pseudotime axis (C) in BAL from HDs and patients with mild or severe COVID-19. Credit: *Science Immunology* (2022). DOI: 10.1126/sciimmunol.add4906

A new study by HSS Research Institute scientists identifies a mechanism by which SARS-CoV-2 induces the inflammatory response in COVID-19 patient lungs, so-called "cytokine storm", that can lead to lasting tissue damage and poor patient outcomes. The lead investigator Dr. Franck J. Barrat and Dr. Lionel B. Ivashkiv at the Hospital for Special Surgery worked in collaboration with Drs. Olivier Elemento and Robert E. Schwartz at Weill Cornell Medicine (WCM) on this study, looking at lung tissue samples and bronchoalveolar lavage from COVID-19 patients.

In a study published September 9 in *Science Immunology*, the investigators outline what controls the cytokine storm by lung-infiltrating macrophages, as these cells are not efficiently infected by SARS-CoV-2.

Researchers found that an immune cell type, called plasmacytoid dendritic cells (pDCs), are infected by SARS-CoV-2 and produce interferons that can provoke epigenetic changes in the nearby macrophages in the lungs of patients. Hence, this priming of macrophages by interferons leads to their exacerbated response to

environmental stimuli, inducing the cytokine storm in the lungs of COVID-19 patients.

This is surprising as interferons and pDCs have been demonstrated to protect patients infected by SARS-CoV-2—but this new research uncovers that they can also provoke damaging cytokine storms.

"There is still a lot we don't know about the pathogenesis of COVID-19, and why macrophages can produce these cytokine storms that can have such dramatic consequences for patients. We hope that this research will bring us closer to that understanding and will lead to better treatment options for patients with severe COVID-19," said Dr. Barrat (Michael R. Bloomberg Chair, Hospital for Special Surgery; Professor of Microbiology and Immunology, Weill Cornell Medicine).

More information: Paôline Laurent et al, Sensing of SARS-CoV-2 by pDCs and their subsequent production of IFN-I contribute to macrophage-induced cytokine storm during COVID-19, *Science Immunology* (2022). DOI: 10.1126/sciimmunol.add4906

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